



## Original article

## Adherence patterns in patients with type 2 diabetes on basal insulin analogues: missed, mistimed and reduced doses

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## Abstract

## Objective:

To describe basal insulin analogue dosing irregularities, the effect of these events on patient functioning, well-being and diabetes management, and the identification of patients most at risk.

## Research design and methods:

The GAPP2 (Global Attitude of Patients and Physicians 2) study was an online multinational cross-sectional study of patients with type 2 diabetes currently treated with basal insulin, and healthcare professionals (HCPs) involved in the care of such patients. Basal insulin adherence patterns were evaluated with respect to three types of dosing irregularity: missed, mistimed ( $\pm 2$  hours from prescribed time), and reduced dose over the last 30 days.

## Results:

A total of 3042 patients treated with basal insulin analogues and 1222 prescribers completed the full survey; 38% of patients reported any type of basal insulin dosing irregularity in the last 30 days. Patients reported missing (22% on  $3 \pm 0.16$  occasions), mistiming (24% on  $4.2 \pm 0.21$  occasions) or reducing (14% on  $4.2 \pm 0.24$  occasions) basal insulin doses, with 15% of patients reporting multiple types of dosing irregularities. For most patients, missed (83%) and mistimed doses (82%) were unintentional, whereas the majority (87%) of patients reducing doses did so intentionally. Patients who intentionally missed or reduced a dose of basal insulin were significantly more likely to have performed this dosing irregularity on multiple occasions. Fifty-three percent of patients increased the frequency of blood glucose monitoring, and 17% of patients extended the duration of more frequent blood glucose monitoring by one or more days as a result of unintentional missed doses. Reduced dosing was highest in a subset of patients reporting self-treated hypoglycaemia.

## Conclusions:

Basal insulin dosing irregularities including missed, mistimed and reduced doses are common. A significant proportion of patients also report undertaking these irregular dosing behaviours at a frequency that would be considered by prescribers to negatively impact diabetes management. This is despite the potential under-reporting due to recall or social bias that may be a limitation of a self-reported survey around these behaviours.

## Introduction

Non-adherence to insulin treatment is one of the most important and poorly understood challenges that continue to impede optimal management of diabetes<sup>1</sup>. The consequences of poor treatment and medication adherence are only now being fully appreciated, with independent effects not just limited to glycaemic control, hypoglycaemia and health costs, but also all-cause mortality<sup>2–6</sup>.

Insulin non-adherence has been reported in up to two-thirds of patients<sup>6–11</sup>, with approximately one-third reporting an average of three episodes of insulin omission/non-adherence within the previous month<sup>11</sup>. Regimen complexity, in terms of the number of the treatments and frequency of administration, is known to have a negative impact on adherence<sup>6,7,12</sup>, as have treatment tolerability issues<sup>13</sup>.

Hypoglycaemia has been one of the principle limitations to insulin treatment<sup>2</sup>. Self-treated (minor) hypoglycaemia has been shown to have serious implications for patient health, psychological well-being, and adherence to treatment regimens<sup>14–16</sup>. Ensuing fear of hypoglycaemia, which is increased in patients experiencing self-treated hypoglycaemia, also negatively influences patient self-management – patients prioritising the immediate avoidance of hypoglycaemia (intentionally missed or reduced doses of insulin)<sup>14</sup> over long-term glycaemic control and prevention of complications. Conversely, increased medication possession ratios (MPR) – a proxy for improved treatment adherence – have been shown to reduce hypoglycaemia incidence and healthcare costs<sup>17–19</sup>. Further, while physicians are generally aware of the problems of insulin specific non-adherence<sup>11,20</sup>, data guiding the identification of non-adherent patients and understanding of non-adherent behaviour is limited.

The objective of the current study was therefore to describe basal insulin analogue adherence pattern, specifically missed, mistimed and reduced doses, and the burden of these events on patient functioning, well-being and diabetes management; examine the relationship of dosing irregularities with hypoglycaemia; and to examine the influence of patient demography, behaviour, treatment, and disease characteristics on the incidence of these dosing irregularities in order to identify a clinically relevant profile of patients most at risk for these behaviours.

## Methods

The GAPP2 (Global Attitudes of Patients and Physicians 2) study was an online multinational cross-sectional study of insulin treated patients with T2DM, and healthcare professionals (primary care practitioners, specialists and nurses) involved in the care of such patients. The survey was conducted in United States, Japan, United Kingdom, Germany, Canada and Denmark.

Approval for the study protocol was obtained from the New England Institutional Review Board (document number 12-027).

## Study design

The items included in the questionnaires were developed from multiple sources including an international steering

committee of clinical diabetes experts, current literature on dosing irregularities and self-treated hypoglycaemia, and from nine previously conducted patient focus groups and interviews involving diabetes patients which were also used to ensure high survey content validity.

The questionnaire was evaluated in two phases prior to distribution. In the first phase, a small sample of pre-recruitment responders completed the prototype questionnaire within each of the participating countries, in the presence of a native speaking researcher. The researcher was present to record any confusion arising during the survey and did not otherwise interact with the responder. This process of cognitive debriefing was used to finalise the language prior to phase 2. Following cognitive debriefing minor edits, which did not specifically affect the questions asked, were implemented, for example the addition of don't know/can't remember as a response option. No questions were removed or significantly altered. In the second phase a small sample (50–100 responders per country) were recruited to participate in the survey. The initial 10 responses from each country were collected and the data and survey mechanism was analysed for sense and logic. The survey was then extended to the full panel of patients and healthcare professionals.

The patient 90-item questionnaire and healthcare professional 58-item questionnaire were both structured in the same way to facilitate subsequent comparison between the two responder groups. Both self-complete surveys employed an adaptive question approach to shorten completion time and minimise responder exposure to redundant questions based on previous responses. Where possible, a 'don't know' was offered as an option so as to avoid forcing responders to make inaccurate judgments. Electronic data logic was performed during the conduction of the survey to ensure that responders did not provide contradictory answers to questions. Data identified as being incomplete (defined as responses that did not reach the end of the survey) was collected but not included in the final analysis.

The definition of self-treated hypoglycaemia was similar in both surveys. In the patient survey, self-treated hypoglycaemia was defined as 'symptoms of low blood sugar such as sweating, weakness, trembling, and difficulty concentrating, which you could treat yourself (for example, by drinking a glass of juice or taking a "sugar pill")'. In the healthcare professional survey, self-treated hypoglycaemia was defined as 'low blood sugar events that the patients can treat themselves, i.e. without medical assistance'. To minimise the impact of recall bias, reporting of self-treated hypoglycaemia and dosing irregularities were restricted to the 30 days prior to the completion of the survey. These basal dosing irregularities included reduced, mistimed [ $\pm 2$  hours from prescribed time in the respondents' judgment] and missed doses. Dose increases were not investigated. Basal insulin analogues were distinguished

from insulin non-analogue preparations in the patient questionnaire on the basis of their appearance (i.e. clear versus cloudy). Data on specific basal insulin products used by respondents was not collected.

When asked about their intentional basal dosing alterations, patients were offered the option of saying that they had been advised to alter their regimen by a healthcare professional. However, when listing other reasons for intentional dosing changes they were not specifically asked if this had or had not been clinically advised as the survey was intended to capture the patient perspective regarding their self-reported adherence behaviour. However, it was assumed that unintentional dosing alterations would be non-advised and that for intentional dosing behaviours certain reasons (excluding advised by a healthcare professional as documented above) would be likely to constitute clinically advisable alterations (my blood sugar was too low; my blood sugar was too high; I had recently exercised; I had skipped a meal; my eating pattern was not as it normally is) and other reasons would not align with clinical recommendations (to reduce the risk of having a low blood sugar; I ran out/was running low on insulin; I was in a social situation where I didn't feel comfortable). A response option for 'other' was also provided.

## Participants

Patients invited to participate in the survey were recruited from an established online general population sample comprising 6.5 million members within the countries surveyed. These panels were identified via an independent research company (Bryter Limited) who contracted commercial research panels such as Research Now, GMI/Lightspeed and WorldOne, etc. The panels were comprised of a representative sample of the online population as a whole for each country in order not to bias the sample to any particular demographic group or respondent profile. Members were recruited from a broad array of online and offline approaches that best represent the local online community as a whole within each country. Recruitment techniques include banner placements on websites, email campaigns, online advertising, blogs, social media, referrals through existing panel members, affiliate marketing (including TV/print) and text (SMS) mobile campaigns.

Potential patients were initially invited by email to participate in the survey based on previous survey evidence of diabetes and age over 40 years; invitations were then randomly distributed. Inclusion criteria were as follows: diagnosis of type 2 diabetes made by a healthcare professional (self-reported); age over 40 years; and current treatment with a long-acting (basal) insulin alone or in combination with a short-acting (bolus) insulin. Patients currently managed with bolus only or premixed insulin were excluded from the survey, as were patients using insulin pumps.

Similarly, healthcare professionals were invited from a panel comprising over 600,000 members in the countries surveyed. Invitations were emailed to random samples within each professional group (primary care, diabetes specialist and nurse). Email responders were screened according to the following study inclusion criteria: minimum 2 years post qualification, minimum of 10 patients treated with insulin analogues per month (every 3 months in Japan and Denmark), and minimum number of patients with type 2 diabetes seen per month; for primary care physicians, the minimum number of patients was 20 (5 in Japan and Denmark to reflect the national situation), and for specialists the minimum number of patients was 40 (30 in Japan and 20 in Denmark).

Non-monetary incentives were offered to patients (equivalent in value to 0.30–1.10 USD per minute) and monetary incentives to healthcare professionals (1.60–4.70 USD per minute), in accordance with local regulations.

Data were stored on secure servers in compliance with the UK Data Protection Act (1998) and collected data was stored by the research company separately from any personal or contact information. Each respondent was issued with a unique URL, which could be used once and electronic data was de-identified with respondents identified by study ID (RESPID) only. The data was analysed on an aggregated level.

In this analysis, we report on the subset of type 2 diabetes patients treated with insulin analogues (patients), and primary care and specialist healthcare professionals (prescribers).

## Primary variables

The primary variables of interest for characterising adherence patterns in patients were: basal insulin dosing irregularities in the past 30 days (frequency of missed doses, mistimed doses [ $\pm 2$  hours from prescribed time in the respondents' judgement], or reduced doses). Dosing irregularities are only reported in basal insulin due to the fact that bolus alterations are common and in many cases based on clinical advice. Additionally the incidence of intentional dosing irregularities and reasons for this behaviour, and the impact of dosing irregularity on functional well-being are reported. For physicians, the primary variable of interest was the level of patient dosing irregularity (missed, mistimed and reduced dose) believed to be of clinical relevance.

## Statistical analysis

Continuous data are described as mean (standard deviation) in tables or mean  $\pm$  standard error in text for normal distributions or median (range) for skewed distributions.

Categorical data are presented using frequencies. Outliers were defined as values lying more than 1.5 interquartile ranges (IQRs) below the first quartile or above the third quartile; and in instances where outlying values exhibited a large degree of influence on the parameter of interest (as assessed by Cook's distance), these values were removed from the analysis.

Group comparisons of continuous data were made using the unpaired *t*-test. Pearson's chi squared test was employed to compare categorical data. In all analyses, level of significance was set at  $\alpha = 0.05$ . Responses identified electronically as incomplete were excluded from the analyses.

CHAID (Chi-squared Automatic Interaction Detection) analysis<sup>21,22</sup> was used to test for interactions between variables and identify which patient factors were most associated with three different types of basal insulin dosing irregularity: missed dose, mistimed dose, and reduced dose. The CHAID tree branches show the proportion of total events (top section of the boxes) and proportion of patients (bottom section of the boxes) with the characteristics described by the branching variables.

Whereas logistic and linear regression models allow assessment of the effects of multiple characteristics simultaneously, the CHAID analysis permits the identification of specific subsets of the sample population reporting disproportionately high frequencies of dosing irregularity. The CHAID analysis constructs prediction trees for each dosing irregularity, where each branch identifies a split condition (based on a response to an explanatory variable) to yield the statistically optimum prediction of characteristics that identifies patients most likely to engage in the dosing irregularity under examination. In order to construct the decision tree, factors from the survey were grouped according to four conceptual domains to provide a structure and informed analysis framework: (1) disease history and management (duration of diabetes, diabetes specific co-morbidity, non-insulin antidiabetes treatments, duration of insulin therapy, insulin regimen, current method of basal insulin administration, number of insulin injections per day, and number of visits to a healthcare professional in the last 12 months); (2) patient behaviours (missed, mistimed or reduced basal insulin doses in the last 30 days; (3) patient perceptions (perceived diabetes control, basal insulin inconvenience, and the extent to which basal insulin interferes with lifestyle and activity, patient satisfaction with current basal insulin treatment, patient comfort with taking insulin, patient guilt or worry about missed doses, patient downplaying or hiding missed doses from healthcare professionals, worry about hypoglycaemia; and (4) patient attributes (age at diagnosis, current age, gender, BMI, current working situation, educational level, lifestyle activity and eating meals at regular times). Bonferroni adjustment was used to correct for multiple splits of a single predictor.

Dosing irregularities were retrospectively defined as an ordinal outcome according to the responses from the prescriber arm of the study on clinical impact: no events (0), one to four irregularities in a 30 day period (1), or five or more irregularities in a 30 day period (2).

All analyses were performed using the statistical package SI-CHAID (Version 4.0.4, Statistical Innovation).

## Results

A total of 1,034,363 individuals (from general population research panels) were invited to participate in the patient survey (initial response rate 9.8%). These general population respondents produced 13,057 eligible patients who met the pre-specified entry criteria, of whom 3587 eligible respondents went on to complete the full survey, response rate 27.5% (Figure 1). Patients treated with insulin analogues comprised 84.8% ( $n = 3,042$ ) of the complete responses received.

In the healthcare professionals group, 36,240 were invited to participate in the survey. Out of 5115 responding to the invitation, 2667 were eligible for survey inclusion, and 1653 completed all questions. Physicians comprised 73.9% ( $n = 1222$ ).

In the results presented only one outlier response was removed in relation to the reported number of mistimed doses in the last 30 days.

Demographic and treatment information for both responder groups are summarised in Table 1.

## Prevalence and incidence of dosing irregularities

A total of 38% of patients reported any type of basal insulin dosing irregularity in the last 30 days. In this time period, 22% of patients reported missing (mean  $3 \pm 0.16$  occasions), 24% mistiming (mean  $4.2 \pm 0.21$  occasions) and 14% reducing (mean  $4.2 \pm 0.24$  occasions) at least one basal insulin dose (Table 2).

Multiple dosing irregularities also occurred: 3% of patients reported having missed, mistimed and reduced a dose of basal insulin; 12% reported performing two out of the three dosing irregularities, and 23% of patients reported a single type of dosing irregularity.

Of those patients who reported dosing irregularities, 17% of patients reported missing, 27% mistiming and 27% reducing their basal insulin dose five times or more. The frequency of missed doses, mistimed doses and reduced doses of basal insulin were similar for patients using basal insulin alone versus those using basal with bolus insulin (Table 3).

Although missed and mistimed doses were usually unintentional (83% and 82% respectively), the majority of patients who reduced their dose of basal insulin did so intentionally. In the last 30 days, 87% of patients who



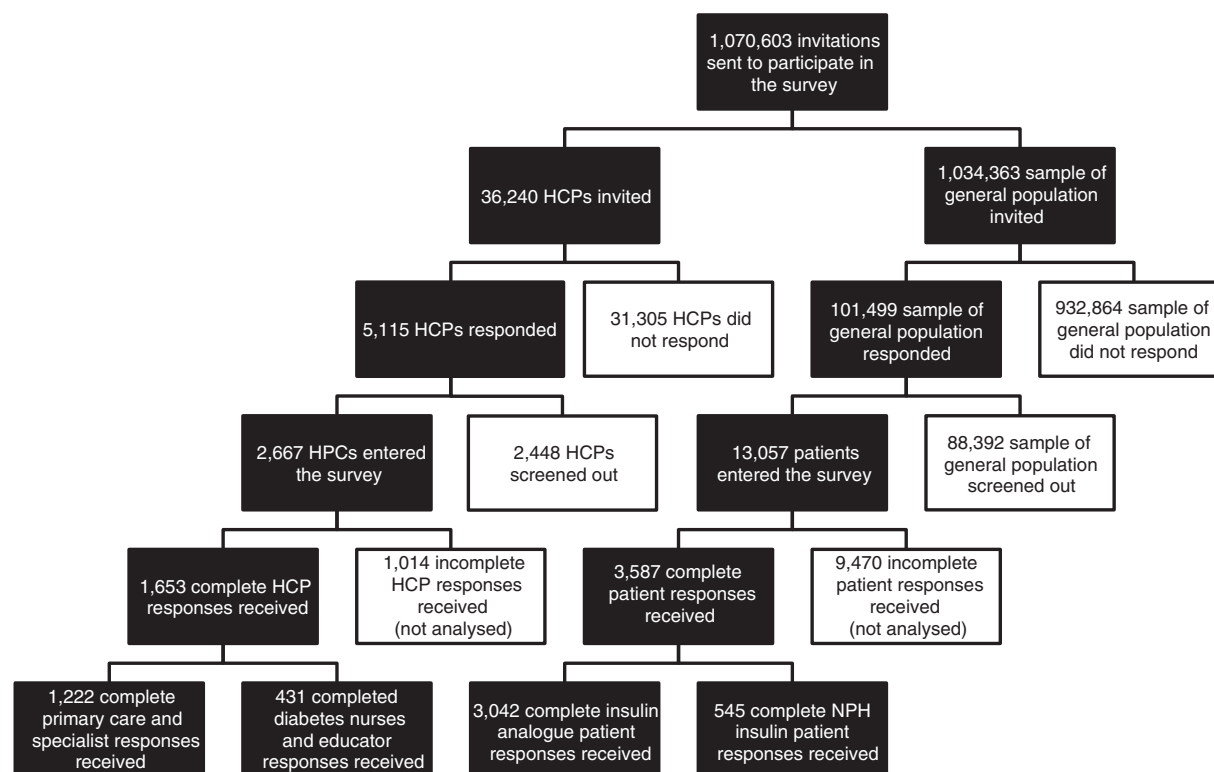


Figure 1. Patient and healthcare professional survey recruitment flow diagram.

had reduced their last dose of basal insulin reported that this was intentional. Patients who intentionally missed or reduced a dose of basal insulin on the last occasion were more likely to have performed this dosing irregularity on multiple occasions over the last 30 days: missed doses ( $5.0 \pm 0.61$  versus  $2.6 \pm 0.14$  occasions in patients intentionally and unintentionally missing their last dose,  $p < 0.001$ ), reduced doses ( $4.3 \pm 0.27$  versus  $3.0 \pm 0.71$  occasions in patients intentionally and unintentionally reducing their last dose,  $p = 0.091$ ) (Table 3). Reasons given for intentionally missing, mistiming or reducing a basal insulin dose include a mixture of those defined as more likely to be in line with clinical advice and those more likely to be contrary to healthcare professional recommendations (Figure 2). The proportions of the reported reasons for intentional adjustments assumed to be contrary to clinical advice based on our definitions were 36% for missed doses, 28% for mistimed doses and 34% for reduced doses.

### Effect of dosing irregularities on diabetes management

Patients who had unintentionally missed doses reported changes to diabetes management and well-being: 53% of patients increased the frequency of blood glucose monitoring, and 17% of patients extended the duration of more

frequent blood glucose monitoring by one or more days; 69% of patients reported being 'more careful with their diabetes management' (28% for a few days or more). When asked, 39% of all patients said they would worry about missing the occasional basal insulin dose; and 37% would feel guilty about an unintentional omission.

Physicians reported that the frequency of basal insulin dosing irregularities in the last 30 days that they perceived to have a significant impact on glucose control was  $4.3 \pm 0.1$  missed,  $5.7 \pm 0.2$  mistimed, or  $5.1 \pm 0.1$  reduced basal insulin doses for patients treated with a basal insulin regimen; and  $4.3 \pm 0.1$  missed,  $5.6 \pm 0.2$  mistimed and  $4.8 \pm 0.1$  reduced basal insulin doses for patients on basal-bolus regimens. Despite acknowledgement of the clinical relevance of irregular dosing, 32% of physicians reported not routinely discussing basal insulin dosing irregularities with their basal insulin patients and 29% did not routinely discuss them with their basal-bolus patients.

### Effect of dosing irregularities on patient functioning

Being required to administer basal insulin at the same prescribed time every day was also reported by patients as having a negative impact on one of several activities in 47% of patients (Figure 3). The negative impact was highest for spontaneous activities such as the ability to stay

Table 1. Patient and physician demographics.

	TOTAL	US	Canada	Japan	UK	Denmark	Germany
<b>PATIENT DEMOGRAPHICS</b>							
Base (n)	3042	1850	156	355	322	57	302
Age (years)	61 (8.12)	62 (7.63)	60 (8.26)	57 (8.12)	60 (8.63)	62 (8.27)	57 (7.75)
Male (%)	59	50	54	85	67	65	70
Duration of diabetes (years)	11 (6.70)	12 (6.56)	12 (8.05)	10 (6.87)	11 (6.45)	11.7 (6.47)	9 (5.94)
Duration of insulin treatment (years)	5 (4.44)	5 (4.46)	5 (4.92)	5 (4.28)	5 (4.28)	7 (5.80)	5 (4.03)
Insulin treatment (%)							
Basal only	48	51	50	43	52	51	33
Basal-bolus	52	49	50	57	48	49	67
Number of basal injections per day	1.3 (1.21)	1.3 (1.04)	1.3 (0.57)	1.3 (0.75)	1.3 (0.69)	1.4 (0.77)	1.7 (2.60)
Perceptions of control (%)							
Poor	10	10	7	21	6	4	5
Moderate	56	58	54	64	53	39	39
Good	34	32	38	15	41	58	56
BMI (kg/m <sup>2</sup> )	34 (19.22)	36 (19.37)	38 (30.75)	26 (13.71)	32 (17.84)	35 (33.89)	32 (7.42)
Number of diabetes complications*, median (range)	2 (0–13)	2 (0–10)	2 (0–11)	1 (0–13)	3 (0–10)	3 (0–8)	3 (0–9)
Education (%)							
Some high school	3	1	1	2	14	5	5
High school graduate	23	21	14	32	22	14	32
Some college (no degree)	23	29	17	17	12	5	8
College (degree)	37	35	34	49	43	63	36
Masters/PhD/Postdoctorate	13	14	34	0	7	6	17
<b>PHYSICIAN DEMOGRAPHICS</b>							
Base (n)	1222	311	202	222	208	70	209
Specialty (%)							
Primary care	55	51	79	40	50	73	51
Specialist	45	49	21	60	50	27	49
Time since qualified (years)	17 (8.17)	17 (7.66)	21 (8.46)	16 (8.54)	14 (7.27)	18 (9.39)	14 (6.32)
Average number of insulin treated patients with T2DM aged 40+							
Primary care	67 (63.42)	89 (67.44)	80 (73.29)	27 (21.30)	70 (60.30)	26 (15.93)	73 (59.91)
Specialist	147 (112.02)	165 (101.48)	130 (81.01)	113 (125.68)	130 (89.05)	69 (28.87)	197 (126.41)

\*Out of a total of 13 listed complications. Continuous variables are given as mean (standard deviation) unless specified.

BMI: body mass index; T2DM: type 2 diabetes mellitus.

overnight without planning (33%), and the ability to go on holiday or to travel (26%).

### Patient characteristics associated with dosing irregularities (CHAID analysis)

For missed dosing, the report of a mistimed dose in the preceding 30 days was identified as the variable most individually associated with an increased risk of missed doses and was therefore the primary differentiator in the CHAID tree (Figure 4a). Eating meals at regular times was identified as the key secondary differentiating variable. For those who had not reported a mistimed dose they were only at an increased risk of reporting a missed dose if they also had irregular mealtimes and had a poor perception of their diabetes control. By contrast, patients who had mistimed a dose in the last 30 days were at increased risk if they did not have regular meals. Additionally if patients had mistimed a dose and did eat regular meals, they were still at increased risk if they were anxious about co-morbidities; or if they were not anxious and female; or if they were not anxious, were male and were also un-satisfied with their

insulin treatment. The characteristics of the patients most at risk of reporting missed doses (defined by the ratio of the proportion of reported missed doses to the population proportion) were those who mistimed a dose, never/rarely ate meals at regular times and were overweight or obese. This group of patients represented 2.6% of the patient sample but accounted for 17.1% of all reported missed doses.

For the mistimed dosing CHAID tree (Figure 4b), the report of a missed dose in the preceding 30 days was identified as the variable most individually associated with increased risk of mistimed doses. Eating meals at regular times and basal insulin convenience were identified as the key secondary differentiating variables. For those who had not reported a missed dose they were only at an increased risk of mistimed doses if they never/rarely or sometimes ate meals at regular times, and had a poor perception of their diabetes control; or they had a moderate perception of diabetes control in combination with administering their basal insulin by a vial and having a barely active lifestyle. For patients reporting missed doses in the preceding 30 days, they were at increased risk of mistiming doses if they also reported that basal insulin was inconvenient.

Table 2. Basal insulin dosing irregularities in the previous 30 days.

	Global	USA	Canada	Japan	UK	Denmark	Germany
<b>MISSED A DOSE OF BASAL INSULIN</b>							
Effective base (n)	2883	1754	151	334	315	57	272
Proportion of patients (%)	22% (647)	26% (455)	23% (34)	15% (49)	16% (51)	12% (7)	19% (51)
Mean number of missed doses	3 (4.04)	3.2 (4.20)	3.2 (5.42)	3.1 (4.51)	2.1 (2.18)	1.1* (0.38)	2.3 (2.11)
5+ times in past 30 days (%)*	3.7% (107)	4.7% (82)	2.6% (4)	3.0% (10)	1.6% (5)	0% (–)	2.2% (6)
<b>MISTIMED A DOSE OF BASAL INSULIN</b>							
Effective base (n)	2741	1650	148	334	305	50	254
Proportion of patients (%)	24% (656)	26% (423)	26% (38)	18% (60)	20% (62)	20% (10)	25% (63)
Mean number of mistimed doses	4.2 (5.41)	4.2 (5.30)	4.8 (6.25)	5.4 (5.46)	3.7 (4.70)	3.7* (3.59)	3.9 (6.38)
5+ times in past 30 days (%)*	6.5% (177)	6.5% (108)	6.8% (10)	8.1% (27)	4.3% (13)	6.0% (3)	6.3% (16)
<b>REDUCED A DOSE OF BASAL INSULIN</b>							
Effective base (n)	2913	1792	152	345	312	51	261
Proportion of patients (%)	14% (417)	15% (260)	13% (19)	11% (37)	18% (56)	12% (6)	15% (39)
Mean number of reduced doses	4.2 (5.00)	4.3 (5.19)	2.8* (2.32)	3.8 (2.98)	3.8 (5.15)	1.3* (0.52)	5.3 (6.05)
5+ times in past 30 days (%)*	3.8% (111)	4.0% (72)	2.0% (3)	3.5% (12)	3.5% (11)	0% (–)	5.0% (13)

Continuous variables are given as mean (standard deviation) unless specified.

\*Small base size.

Table 3. Basal insulin dosing irregularities in the previous 30 days, by insulin regimen and patient intention.

	Dosing irregularities by insulin regimen			Basal insulin Dosing irregularities by patient intention		
	Basal insulin only	Basal and bolus insulin	p value	Intentionally dose irregularly last time they did this	Did not intentionally dose irregularly last time they did this	p value
<b>MISSED A DOSE OF BASAL INSULIN</b>						
Effective base (n)	1399	1484		178	1176	
Proportion of patients (%)	24% (329)	21% (318)	0.179	63% (112)	45% (527)	<0.001
Mean number of missed doses	2.9 (3.39)	3.2 (4.61)	0.347	5.0 (6.47)	2.6 (3.14)	<0.001
5+ times in past 30 days (%)	3.7% (52)	3.7% (55)	0.987	17.4% (31)	6.3% (74)	<0.001
<b>MISTIMED A DOSE OF BASAL INSULIN</b>						
Effective base (n)	1338	1403		237	1097	
Proportion of patients (%)	26% (353)	22% (303)	0.003	50% (119)	46% (509)	0.286
Mean number of mistimed doses	4.2 (5.03)	4.3 (5.83)	0.816	4.8 (5.22)	4.1 (5.33)	0.191
5+ times in past 30 days (%)	7.3% (98)	5.6% (79)	<0.071	16.9% (40)	12.1% (133)	0.048
<b>REDUCED A DOSE OF BASAL INSULIN</b>						
Effective base (n)	1405	1508		856	207	
Proportion of patients (%)	14% (197)	15% (220)	0.662	43% (364)	21% (44)	<0.001
Mean number of reduced doses	4.2 (4.91)	4.2 (5.09)	1	4.3 (5.07)	3.0 (4.69)	0.091
5+ times in past 30 days (%)	3.6% (51)	4.0% (60)	0.623	12.0% (103)	2.9% (6)	<0.001

Continuous variables are given as mean (standard deviation) unless specified.

If they had missed a dose but did not think that basal insulin was inconvenient, they remained at increased risk if they had reduced a dose of their basal insulin; or if they had not reduced a dose but had thought they had poor or moderate diabetes control. The patient sub-set most at risk of mistimed doses (accounting for 17% of mistimed doses) were those patients who perceived basal insulin dosing to be inconvenient and reported missed doses (4% of the total patient sample).

For reduced dosing, the primary variable identified in the CHAID tree (Figure 4c), i.e. the variable most individually associated with an increased risk of reduced doses, was self-treated hypoglycaemia in the preceding 30 days. Mistiming a dose was identified as the key secondary

differentiating variable. For those who had not experienced a self-treated hypoglycaemic event the only groups more associated with reduced doses were those aged 50 years and over and those aged 40–49 years who had also been on insulin for more than 2 years and who had also missed a dose. For those reporting self-treated hypoglycaemia, those patients who had mistimed a dose and did not feel guilty about missed doses were at increased risk of reducing doses. Additionally, for those reporting self-treated hypoglycaemia that had not mistimed a dose were at increased risk of reporting reduced doses if they administered their insulin by a pen; or if they did not use a pen but also reported nerve damage. The subset of patients with the highest risk of reduced dosing was those with a history

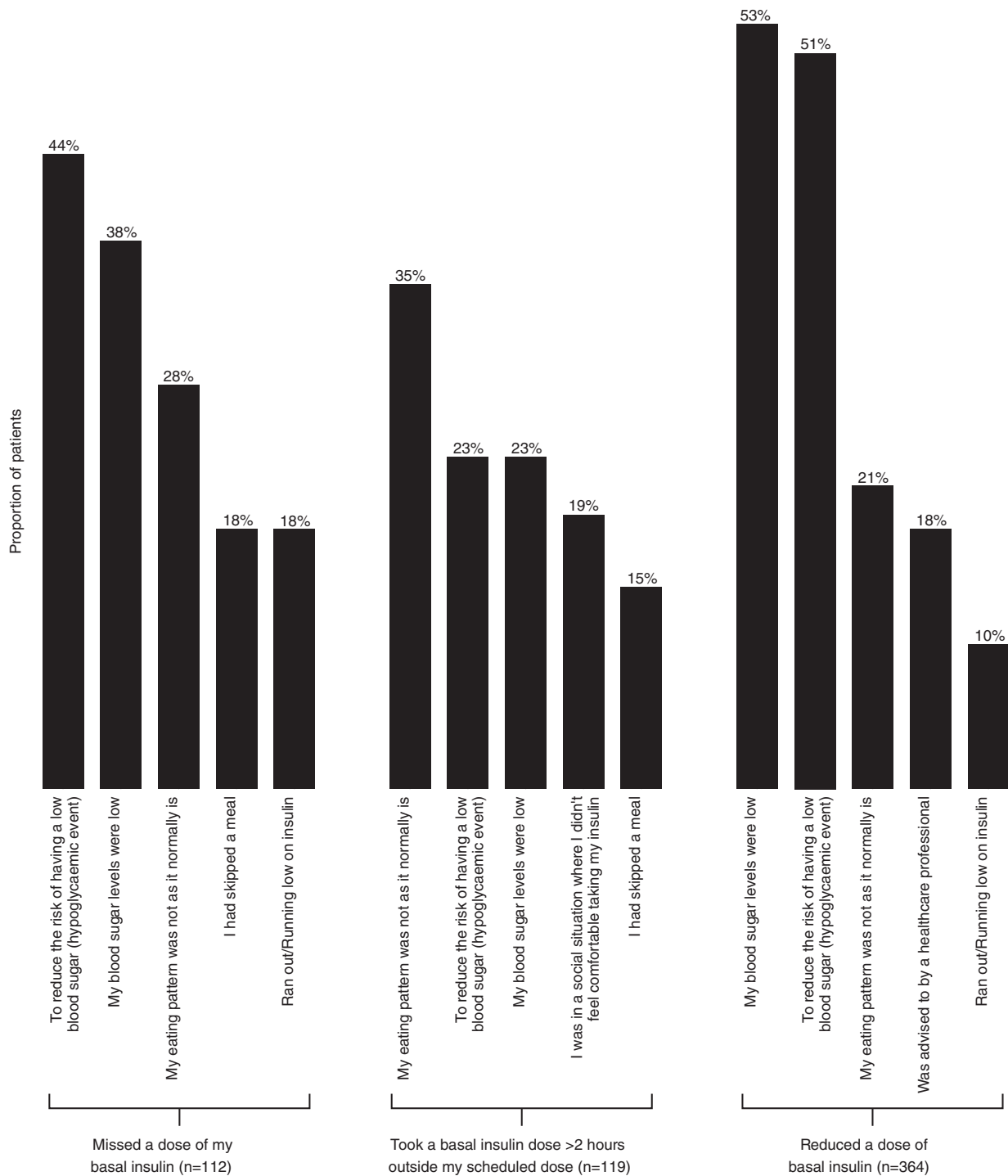


Figure 2. The five most common reasons for intentional dosing irregularities.

of self-treated hypoglycaemia, mistimed doses, did not feel guilty about missing the occasional basal insulin dose and were aged 50 and over. This high risk group comprised of 2.3% of the sample but accounted for 10% of reduced dosing events.

Taking into account the three CHAID analyses and the characteristics entered into them for basal dosing

irregularities, the profile of patients who are at increased risk of missed/mistimed or reduced doses show some key attributes some of which are common across the individual irregularities. These factors may act as simple and useful indicators for clinical practice to aid the identification of patients who dose irregularly. These include reports of at least one dosing irregularity (those that report one type of



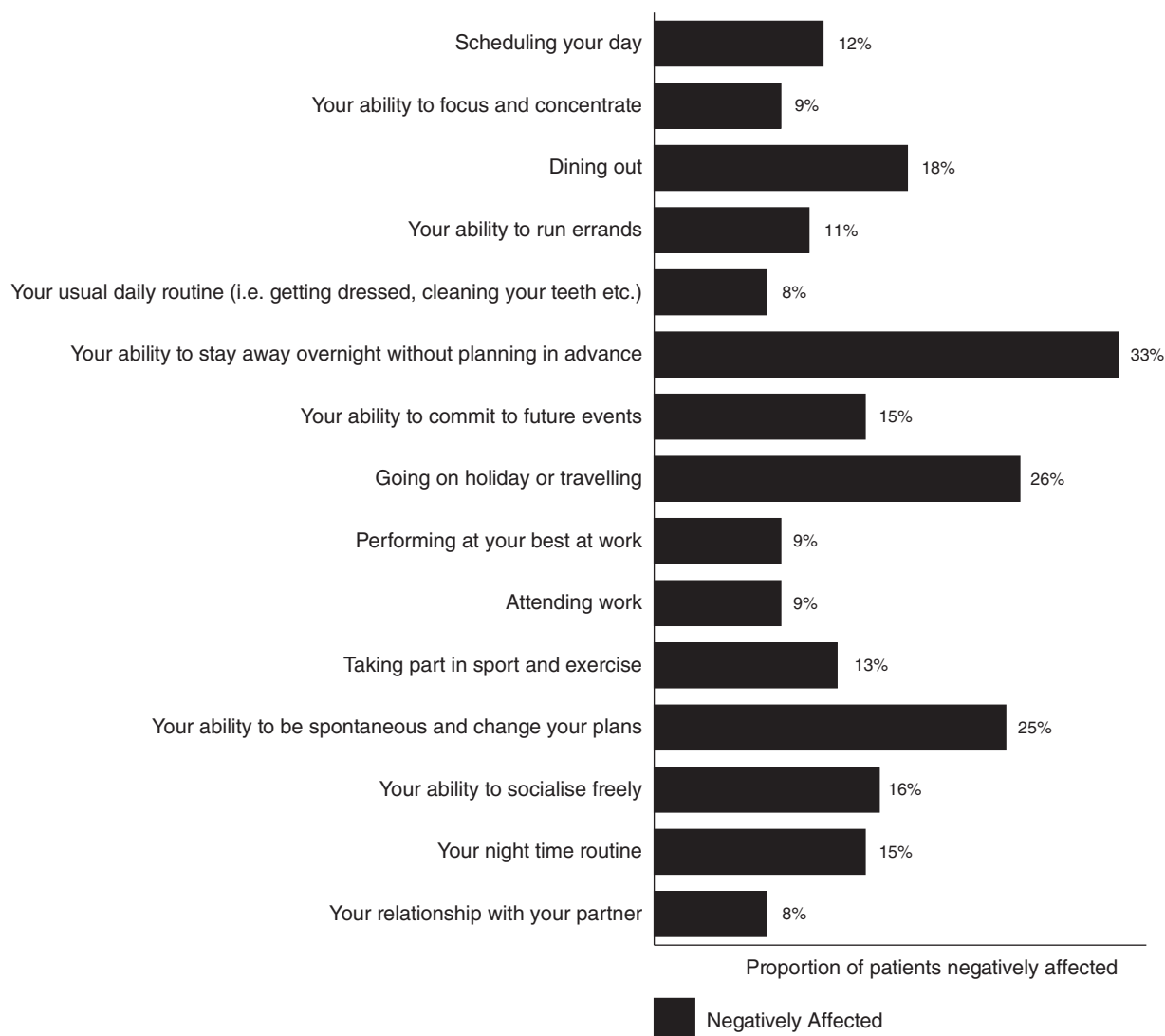


Figure 3. The effect of having to take basal insulin at the prescribed time every day on patient well-being and functioning.

irregularity are often at increased risk of reporting another), poor perceived diabetes control, irregular meal-times, the perception that basal insulin is inconvenient and self-treated hypoglycaemia.

## Discussion

This is the first time that intentional non-adherent dosing behaviour has been shown to be associated with episodes of self-treated hypoglycaemia. This large multinational cross-sectional survey shows that more than a third of patients report one or more basal insulin analogue dosing irregularities comprising missed, mistimed or reduced doses. These dosing irregularities were usually unintentional; in contrast, reducing doses of the basal insulin analogue was performed intentionally by over four fifths of patients

reporting this type of dosing irregularity often for clinically inadvisable reasons. Furthermore, a substantial proportion of patients reported a frequency of dosing irregularities at a level that physicians perceived would have a negative impact on diabetes management. Despite the prevalence of dosing irregularities, however, 32% of prescribers did not routinely discuss these basal adherence patterns with their basal only patients (29% with their basal-bolus patients). Considering these results in the context of the wider type 2 diabetes population suggests that there is a sub-population of insulin analogue users who repeatedly dose irregularly at a level which has the potential to affect glucose control and long-term outcomes<sup>23</sup>.

There appears to be good agreement with the adherence patterns, in this case basal dosing irregularities, reported in this study, and those previously reported in the literature. In a mixed population of patients with type 1 and type 2



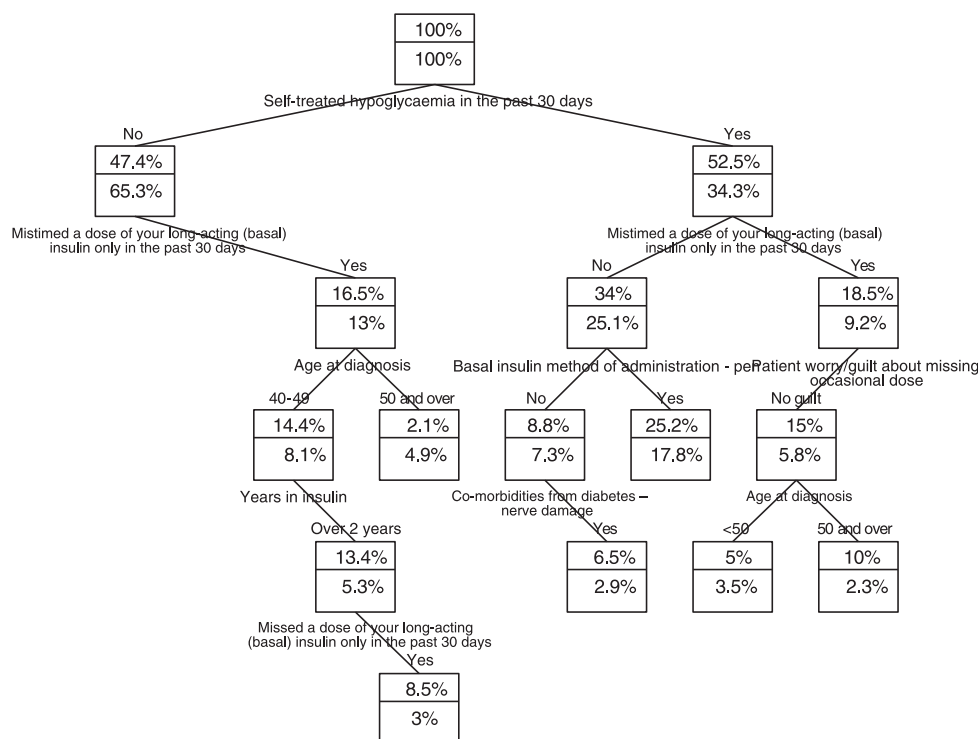
**Figure 4.** The CHAID tree showing combinations of patient characteristics that are associated with increased risk of (a) missed, (b) mistimed; and (c) reduced doses of basal insulin within the previous 30 days.

diabetes, intentional insulin omission was reported by more than half of respondents, with 20% of respondents reporting regular omission over an undefined time interval<sup>24</sup>. In a more recent survey, one third of patients with type 1 and type 2 diabetes reported insulin omission/non-adherence on an average of 3.3 days within the previous month<sup>11</sup>. Although these studies did not evaluate the effect of missed, mistimed and reduced basal insulin

dosing specifically, non-adherence to insulin has been shown to be associated with worse glycaemic control<sup>6,7,10,25–27</sup> and mortality<sup>5</sup>.

Treatment adherence is also commonly assessed through use of the MPR, the ratio of days' medication is supplied over a defined time interval. The MPR for insulin use in patients with type 2 diabetes has previously been reported to be within the range of 58–77%<sup>6,7,27,28</sup>.

(c)



- Top sections show proportion of total events
- Bottom sections show proportion of patients

Figure 4. Continued.

However, despite the non-adherence levels recorded by MPR and the frequency of their use, the measure is likely to include some element of insulin wastage, would not be able to detect mistimed doses and would also be unable to differentiate between missed doses and reduced doses. Interestingly, while the three different dosing irregularities reported appear to be closely interlinked they are nevertheless unique behavioural entities and should be measured as such. In particular, although missed and mistimed doses were clearly associated with each other and poor self-perception of diabetes control; missed doses were more clearly associated with whether or not patients ate meals at regular times, whereas mistimed doses were more strongly associated with perceived insulin inconvenience.

These findings add further evidence that self-treated hypoglycaemia can result in prolonged periods of detrimental self-management behaviour<sup>14,29,30</sup>, particularly in a sub-group of patients such as those who proactively alter their regimen to reduce hypoglycaemic risk. Previously published studies have reported that patients required an average of 5.6 extra blood glucose test strips in the week following a non-severe hypoglycaemic event, and that 25% of patients reduced the dose of insulin<sup>16</sup>. The causality of the association between reduced dosing and self-treated hypoglycaemia cannot be determined from the cross-section survey data available. However, when asked

about the reasons behind intentional dosing irregularities the two most frequently reported reasons were low blood sugar and hypoglycaemia risk reduction (Figure 2), i.e. reasons that relate to both pre- and post-hypoglycaemia alterations. Indeed, this association between self-treated hypoglycaemia and reduced dosing may well explain the lower MPRs reported with insulin compared to oral agents and GLP-1 analogues<sup>7,28</sup> – with some insulin treated patients reducing doses of prescribed insulin in an attempt to mitigate more frequent episodes of hypoglycaemia by maintaining a higher blood glucose level, as has been noted in previous studies<sup>31,32</sup>. Interestingly, Donnelly *et al.*<sup>6</sup> reported a tendency for poorly adherent patients to be prescribed larger quantities of insulin, perhaps in an attempt to improve glycaemic control in the context of poor adherence. The present study suggests that in addition to some inappropriate dosing behaviour on the part of the patient, there may also be an inappropriate response by the physician (increasing prescribed dose) that would fail to address the underlying issue of non-adherence (i.e. intentional pre-hypoglycaemia dose reduction by the patient).

Previously reported risk factors for insulin omission/non-adherence include male gender, younger age, more frequent hypoglycaemia, those who regarded insulin adherence as less important, as well as those who were

more concerned about perceived lifestyle changes, dissatisfaction with the inflexibility of the injection regimen, interference of injection with daily patient activities and causing the patient embarrassment<sup>33</sup>. Other authors have similarly reported associations of poor adherence with patients being professionally active (currently working), not feeling confident about the future, and lack of family and social support<sup>9</sup>. Notably, patients tend to be significantly less satisfied with insulin treatment than physicians<sup>11</sup>. The present study goes one step further in identifying specific subsets of patients based on demographic, disease, treatment and behavioural variables – all of which are consistent with the literature. The present study showed that overweight patients with irregular meal times were most at risk of missing doses, and that patients who perceived basal insulin to be inconvenient were most likely to have mistimed doses. These patient characteristics could be easily identified during clinical consultations, and would alert the physician to possible insulin dosing irregularities and the potential need to re-educate patients or introduce other counter-measures. The finding of an association between self-treated hypoglycaemia and reduced dosing also reinforces the need for healthcare providers to carefully evaluate patients' history of hypoglycaemia, and to try to identify antecedents and recommend appropriate changes to treatment.

As the consequences of irregular dosing are likely to increase in patients reporting multiple types or high frequencies of dosing irregularities, these would be expected to benefit from targeted diabetes management interventions. Particularly, those who intentionally alter their insulin dosing, as our analysis shows that they undertake these behaviours on a more regular basis than those who do not. The present study also shows that, although patients may recognise the potential implications of missed doses for the management of their diabetes, they remain unable to adhere to strict treatment regimens, and adhering to these strict regimens also negatively impacted patients' functional and emotional well-being.

However, there are several limitations to the study. As has been discussed, this is a cross-sectional study, which means that we are unable to attribute a causal effect between any of the associations reported, or determine in which sequence the reported associations occurred. In addition, the sample of respondents was non-randomised although they were targeted via general population research panels and not through patient specific channels in an attempt to minimise some elements of selection bias. This recruitment methodology, however, led to an initial response rate that may be perceived as low but was in line with initial estimations used as part of the sample size calculations and the complete response rate among those eligible was 27.4%. Additionally, the CHAID analysis undertaken is a multivariate technique which also helps to mitigate the effect of other recorded respondent

variables, although the potential role of unidentified confounders still cannot be excluded.

As the survey was focused on insulin analogue users the results of the survey may not be generalisable to patients using other insulin preparations, and though the survey sought to include countries with different cultural and ethnic backgrounds the largest groups of respondents were from Western countries. In addition, the survey was conducted online, which may have led to an over-representation of some key responder groups, for example: younger age group, those in employment and those living in non-isolated situations. Differences in online penetration in the participating countries may also be a potential confounder. At present, the effect of ethnicity and cultural factors on adherence remains poorly understood<sup>34,35</sup>.

It is also likely that the reported basal dosing irregularities are underestimated as the patient survey was self-completed and reports were based on patient judgement which may have led to incorrect classifications. Additionally, recall bias and social bias may also have led to an underestimation of dosing irregularities particularly given that dosing irregularities may be perceived as potentially inappropriate medication taking behaviour. Social bias may also have played a role in some of the prescriber data reported, particularly in relation to the subjective reporting of the frequency of discussion of dosing irregularities in consultation. In this case it should also be noted that the depth of conversation around these issues reported was not further investigated. However, given that the research panels were recruited to be representative of the online community; the online penetration in the surveyed countries was judged to be broadly in line prior to initiation; dosing irregularity definitions were always provided in the questionnaires and that both patients and prescribers were informed that results were confidential and that data is only presented in these analyses focusing on a 30 day period, these biases may have had limited effect.

Yet, despite these findings, future research is required which should focus on interventions that address both the reasons for regular and intentional basal insulin dosing irregularities highlighted in this study, and establishing causality between basal dosing adherence patterns and self-treated hypoglycaemia.

## Conclusion

Basal insulin dosing irregularities including missed, mistimed and reduced doses are common in patients using insulin analogue regimens, and a significant proportion of patients undertake irregular dosing behaviour at a frequency that would be considered by prescribers to negatively impact diabetes management. Clinicians should focus on identifying patients with a higher likelihood of dosing irregularities including those that report self-treated

hypoglycaemia (most highly associated with reduced doses), not having regular mealtimes and poor self-perception of their diabetes control (missed and mistimed doses). Patient concerns about lifestyle interference and insulin treatment burden related to fixed administration times should also be taken into consideration. The results add to a growing body of evidence supporting continued efforts to refine insulin therapy and treatment regimens in terms of safety, simplicity and convenience.

## Transparency

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The GAPP2 study was funded by Novo Nordisk A/S. The role of the sponsor was to appoint an independent medical communications company (FTI Consulting) and research company (Bryter Research). All authors have been involved in the design, conduct, and interpretation of the study. M.B. was involved in preparing the manuscript. A.H.B. and A.R. have reviewed the manuscript for scientific content.

### Declaration of financial/other relationships

M.B. and A.H.B. have received consulting fees and support for travel to meetings from Novo Nordisk in association with the GAPP2 study. A.R. is an employee of Novo Nordisk A/S.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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